CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: **074790**

Trade Name : KETOROLAC TROMETHAMINE TABLETS USP

Generic Name: Ketorolac Tromethamine Tablets USP 10mg

Sponsor : Roxane Laboratories, Inc.

Approval Date: June 26, 1997

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APPLICATION 074790

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074790

APPROVAL LETTERS

ANDA 74-790

JUN 26 1997

Roxane Laboratories, Inc.
Attention: Sue T. Bastaja
P.O. Box 16532
Columbus, OH 43216-6532

Dear Madam:

This is in reference to your abbreviated new drug application dated November 20, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ketorolac Tromethamine Tablets USP, 10 mg.

Reference is also made to your amendments dated December 6, 1995, June 3, 1997 and June 16, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Ketorolac Tromethamine Tablets USP, 10 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Toradol® Tablets, 10 mg of Syntex Laboratories, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

6/26/97

Douglas L. Spoon
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074790

FINAL PRINTED LABELING

KETOROLAC TROMETHAMINE TABLETS USP 10 mg

WARNING

Ketorolac tromethamine, a nonsteroidal anti-inflammatory drug (NSAID), is indicated for the short-term (up to 5 days) management of moderately severe, acute pain, that requires analgesia at the opioid level. It is NOT indicated for minor or chronic painful conditions. Ketorolac tromethamine is a potent NSAID analgesic, and its administration carries many risks. The resulting NSAID-related adverse events can be serious in certain patients for whom ketorolac tromethamine is indicated, especially when the drug is used inappropriately. Increasing the dose of ketorolac tromethamine beyond the label recommendations will not provide better efficacy but will result in increasing the risk of developing serious adverse events.

GASTROINTESTINAL EFFECTS

- Ketorolac tromethamine can cause peptic ulcers, gastrointestinal bleeding, and/or perforation. Therefore, ketorolac tromethamine is CONTRAINDICATED in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding.

RENAL EFFECTS

- Ketorolac tromethamine is CONTRAINDICATED in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion (see WARNINGS).

RISK OF BLEEDING

- Ketorolac tromethamine inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis, and those at high risk of bleeding (see WARNINGS and PRECAUTIONS).
- Ketorolac tromethamine is CONTRAINDICATED as prophylactic analgesic before any major surgery, and is CONTRAINDICATED intra-operatively when hemostasis is critical because of the increased risk of bleeding.

HYPERSENSITIVITY

- Hypersensitivity reactions, ranging from bronchospasm to anaphylactic shock, have occurred and appropriate counteractive measures must be available when administering the first dose of ketorolac tromethamine-IV/IM (see CONTRAINDICATIONS and WARNINGS). Ketorolac tromethamine is CONTRAINDICATED in patients with previously demonstrated hypersensitivity to ketorolac tromethamine, or allergic manifestations to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).

LABOR, DELIVERY, AND NURSING

- The use of ketorolac tromethamine in labor and delivery is CONTRAINDICATED because it may adversely effect fetal circulation and the uterus.
- The use of ketorolac tromethamine is CONTRAINDICATED in nursing mothers because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates.

CONCOMITANT USE WITH NSAIDs

- Ketorolac tromethamine is CONTRAINDICATED in patients currently receiving ASA or NSAIDs because of the cumulative risk of inducing serious NSAID-related side effects.

DOSAGE AND ADMINISTRATION

KETOROLAC TROMETHAMINE TABLETS

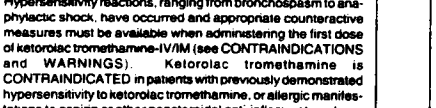
- Ketorolac tromethamine tablets are indicated only as continuation therapy to ketorolac tromethamine-IV/IM, and the combined duration of use of ketorolac-IV/IM and ketorolac tromethamine tablets is not to exceed 5 (five) days, because of the increased risk of serious adverse events.
- The recommended total daily dose of ketorolac tromethamine tablets (maximum 40 mg) is significantly lower than for ketorolac tromethamine-IV/IM (maximum 120 mg) (see DOSAGE and ADMINISTRATION and *Transition from Ketorolac Tromethamine-IV/IM to Ketorolac Tromethamine Tablets*).

SPECIAL POPULATIONS

- Dosage should be adjusted for patients 65 years or older, for patients under 50 kg (110 lbs.) of body weight (see DOSAGE and ADMINISTRATION), and for patients with moderately elevated serum creatinine (see WARNINGS). Doses of ketorolac tromethamine-IV/IM are not to exceed 60 mg (total dose per day) in these patients.

DESCRIPTION

Ketorolac tromethamine is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs). The chemical name for ketorolac tromethamine is (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol and has the following structural formula:



$(C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3)$

Ketorolac tromethamine is a racemic mixture of [-]S and [+]R ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. Ketorolac tromethamine has a pKa of 3.5 and an n-octanol/water partition coefficient of 0.26. The molecular weight of ketorolac tromethamine is 376.41.

Each tablet for oral administration contains 10 mg ketorolac tromethamine, the active ingredient, with lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The white film-coating contains hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide.

The tablets are printed with black ink which includes FD&C Red #40, FD&C Blue #2, FD&C Yellow #6 aluminum lakes, and black iron oxide as the colorants.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID). Ketorolac tromethamine inhibits synthesis of prostaglandins and may be considered a peripherally acting analgesic. The biological activity of ketorolac tromethamine is associated with the S form. Ketorolac tromethamine possesses no sedative or anxiolytic properties.

Pain relief was statistically different after ketorolac tromethamine dosing from that of placebo at ½hour (the first time point at which it was measured) following the largest recommended doses of ketorolac tromethamine, and by 1 hour following the smallest recommended doses. The peak analgesic effect occurred within 2 to 3 hours and was not statistically significantly different over the recommended dosage range of ketorolac tromethamine. The greatest difference between large and small doses of ketorolac tromethamine by either route was in the duration of analgesia.

Pharmacokinetics

Ketorolac tromethamine is a racemic mixture of [-]S and (+)R-enantiomeric forms, with the S-form having analgesic activity.

Comparison of IV, IM, and Oral Pharmacokinetics

The pharmacokinetics of ketorolac tromethamine, following IV, IM, and oral doses, are compared in Table 1. The extent of bioavailability following administration of the oral and IM forms of ketorolac tromethamine was equal to that following an IV bolus.

TABLE 1

Table of Approximate Average Pharmacokinetic Parameters (Mean ± SD)

Following Oral, Intramuscular and Intravenous Doses of Ketorolac Tromethamine

	Oral†	Intramuscular*		
Pharmacokinetic Parameter (units)	10 mg	15 mg	30 mg	60 mg
Bioavailability (extent)	100%	100%	100%	100%
T_{max}[1] (min)	44±34	33±21***	44±25	33±21***
C_{max}[2] (mcg/mL) [single dose]	0.87±0.27	1.14±0.37***	2.42±0.68	4.56±1.27***
C_{max} (mcg/mL) [steady state ave]	1.06±0.36***	1.56±0.64***	3.11±0.87***	N/A**
C_{min}[3] (mcg/mL) [steady state ave]	0.76±0.07***	0.47±0.13***	0.93±0.76***	N/A
C_{av}[4] (mcg/mL) [steady state ave]	0.90±0.39***	0.94±0.75***	1.86±0.58***	N/A
V(ß)[5] (L/kg)	0.175 ± 0.039			

	Intravenous Bolus‡	
Pharmacokinetic Parameter (units)	15 mg	30 mg
Bioavailability (extent)	100%	100%
T_{max}[1] (min)	1.1±0.7***	2.9±1.8
C_{max}[2] (mcg/mL) [single dose]	2.47±0.51***	4.85±0.95
C_{max} (mcg/mL) [steady state ave]	3.08±1.11***	6.05±2.61
C_{min}[3] (mcg/mL) [steady state ave]	0.61±0.21***	1.04±0.35
C_{av}[4] (mcg/mL) [steady state ave]	1.89±0.30***	2.17±0.58
V(ß)[5] (L/kg)	0.210 ± 0.044	

% Dose metabolized = <50 — % Dose excreted in feces = 5

% Dose excreted in urine = 91 — % Plasma protein binding = 99

†Derived from PO pharmacokinetic studies in 77 normal healthy volunteers.

*Derived from IM pharmacokinetic studies in 54 normal volunteers.

‡Derived from IV pharmacokinetic studies in 34 normal volunteers

† † Not applicable because 60 mg is only recommended as a single dose.

**Mean value was simulated from observed plasma concentration data and standard deviation was simulated from percent coefficient of variation for observed C_{max} and t_{max} data.

[1]Time to peak plasma concentration — [4]Average plasma concentration

[2]Peak plasma concentration — [5]Volume of distribution

[3]Trough plasma concentration

Linear Kinetics

Following administration of single oral, IM, or IV doses of ketorolac tromethamine, in the recommended dosage ranges, the clearance of the racemate does not change. This implies that the pharmacokinetics of ketorolac tromethamine in humans, following single or multiple IM, IV, or recommended oral doses, are linear. At the higher recommended doses, there is a proportional increase in the concentrations of free and bound racemate.

Binding and Distribution

The ketorolac tromethamine racemate has been shown to be highly protein-bound (99%). Nevertheless, even plasma concentrations as high as 10 mcg/mL will only occupy approximately 5% of the albumin binding sites. Thus, the unbound fraction for each enantiomer will be constant over the therapeutic range. A decrease in serum albumin, however, will result in increased free drug concentrations.

The mean apparent volume (V_d) of ketorolac tromethamine following complete distribution was approximately 13 liters. This parameter was determined from single dose data.

Metabolism

Ketorolac tromethamine is largely metabolized in the liver. The metabolic products are hydroxylated and conjugated forms of the parent drug. The products of metabolism, and some unchanged drug, are excreted in the urine.

Clearance and Excretion

A single-dose study with 10 mg ketorolac tromethamine (n=9) demonstrated that the S-enantiomer is cleared approximately two times faster than the R-enantiomer, and that the clearance was independent of the route of administration. This means that the ratio of S/R plasma concentrations decreases with time after each dose. There is little or no inversion of the R- to S- form in humans. The clearance of the racemate in normal subjects, elderly individuals, and in hepatically and renally impaired patients, is outlined in Table 2.

The half-life of the ketorolac tromethamine S-enantiomer was approximately 2.5 hours (SD ± 0.4) compared with 5 hours (SD ± 1.7) for the R-enantiomer. In other studies, the half-life for the racemate has been reported to lie within the range of 5 to 6 hours.

Table 2

The Influence of Age, Liver and Kidney Function, on the Clearance and Terminal Half-life of Ketorolac Tromethamine (IM[1] and Oral[2])

	Total Clearance (ml/kg/h)[3]		Terminal Half-life (in hours)	
Type of Subjects	IM mean (range)	Oral mean (range)	IM mean (range)	Oral mean (range)
Normal Subjects IM (n=54), mean age=32, range=18-60 Oral (n=77), mean age = 32, range=20-60	0.021 (0.0116-0.045)	0.025 (0.0113-0.039)	5.3 (3.5-9.2)	5.3 (2.6-8.8)
Healthy Elderly Subjects IM (n=13), Oral (n=12) mean age=72, range=65-78	0.019 (0.0113-0.0264)	0.024 (0.0146-0.0334)	7.8 (4.7-13.6)	6.1 (4.3-7.5)
Patients with Hepatic Dysfunction IM and Oral (n=7), mean age = 51, range = 43-64	0.024 (0.0113-0.0356)	0.033 (0.0113-0.051)	5.4 (2.7-8.9)	4.5 (1.5-7.5)
Patients with Renal Impairment IM (n=29), Oral (n=9) mean creatinine 1.9-5.8 mg/dl, mean age 49th=44, range=25-71 mean age renal=57, range=38-76	0.013 (0.005-.0013)	0.014 (0.007-.0.057)	19.7 (5.9-19.2)	19.2 (3.4-18.9)
Renal Dialysis Patients IM and Oral (n=9) mean age=40, range=27-63	0.014 (0.0053-0.0235)	-	13.5 (8.8-38.1)	-

[1]Estimated from 30 mg single IM doses of ketorolac tromethamine

[2]Estimated from 10 mg single oral doses of ketorolac tromethamine

[3]Liters/hour/kilogram.

IV administration: In normal subjects (n=37), the total clearance of 30 mg IV administered ketorolac tromethamine was 0.030 (0.017-0.051) L/h/kg. The terminal half-life was 5.6 (4.0-7.9) hours.

Accumulation

Ketorolac tromethamine administered as an IV bolus, every 6 hours, for 5 days, to healthy subjects (n=13), showed no significant difference in C_{max} on Day 1 and Day 5. Trough levels averaged 0.29 mcg/mL (SD ± 0.13) on Day 1 and 0.55 mcg/mL (SD ± 0.23) on Day 6. Steady-state was approached after the fourth dose.

Accumulation of ketorolac tromethamine has not been studied in special populations (elderly patients, renal failure patients, or hepatic disease patients).

Effect of Food

Oral administration of ketorolac tromethamine after a high fat meal resulted in decreased peak and delayed time-to-peak concentrations of ketorolac tromethamine by about 1 hour. Antacids did not affect the extent of absorption.

Kinetics in Special Populations

Elderly Patients

Based on single-dose data only, the half-life of the ketorolac tromethamine racemate increased from 5 to 7 hours in the elderly (65 to 78 years) compared with young healthy volunteers (24 to 35 years) (See Table 2). There was little difference in the C_{max} for the two groups (elderly, 2.52 mcg/mL ± 0.77; young, 2.99 mcg/mL ± 1.03) (see **PRECAUTIONS - Use in the Elderly**).

Renally Impaired Patients

Based on single-dose data only, the mean half-life of ketorolac tromethamine in renally impaired patients is between 6 and 19 hours, and is dependent on the extent of the impairment. There is poor correlation between creatinine clearance and total ketorolac tromethamine clearance in the elderly and populations with renal impairment (r=0.5).

In patients with renal disease, the AUC of each enantiomer increased by approximately 100% compared with healthy volunteers. The volume of distribution doubles for the S-enantiomer and increases by 1/5th for the R-enantiomer. The increase in volume of distribution of ketorolac tromethamine implies an increase in unbound fraction.

The AUC ratio of the ketorolac tromethamine enantiomers in healthy subjects and patients remained similar, indicating there was no selective excretion of either enantiomer in patients compared to healthy subjects (see **WARNINGS - Renal Effects**).

Hepatic Effects

There was no significant difference in estimates of half-life, AUC, C_{max}, in 7 patients with liver disease compared to healthy volunteers (see **PRECAUTIONS - Hepatic Effects**).

Clinical Studies

The analgesic efficacy of intramuscularly, intravenously and orally administered ketorolac tromethamine was investigated in two postoperative pain models: general surgery (orthopedic, gynecologic and abdominal) and oral surgery (removal of impacted third molars). The studies were double-blind, single- and multiple-dose, parallel trial designs, in patients with moderate to severe pain at baseline. Ketorolac tromethamine-IV/IM was compared as follows: IM to meperidine or morphine administered intramuscularly, and IV to morphine administered either directly IV or through a PCA (Patient-Controlled Analgesia) pump.

Short Term Use (up to 5 days) Studies

In the comparisons of intramuscular administration during the first hour, the onset of analgesic action was similar for ketorolac tromethamine and the narcotics, but the duration of analgesia was longer with ketorolac tromethamine than with the opioid comparators meperidine or morphine.

In a multi-dose, postoperative (general surgery) double-blind trial of ketorolac tromethamine-IM 30 mg versus morphine 6 and 12 mg IM, each drug given on an "as needed" basis for up to 5 days, the overall analgesic effect of ketorolac tromethamine-IM 30 mg was between that of morphine 6 and 12 mg. The majority of patients treated with either ketorolac tromethamine or morphine were dosed for up to 3 days; a small percentage of patients received 5 days of dosing.

In clinical settings where perioperative morphine was allowed, ketorolac tromethamine-IV 30 mg, given once or twice as needed, provided analgesia comparable to morphine 4 mg IV once or twice as needed.

There was relatively limited experience with 5 consecutive days of ketorolac tromethamine-IV use in controlled clinical trials, as most patients were given the drug for 3 days or less. The adverse events seen with IV-administered ketorolac tromethamine were similar to those observed with IM-administered ketorolac tromethamine, as would be expected based on the similar pharmacokinetics and bioequivalence (AUC, clearance, plasma half-life) of IV and IM routes of ketorolac tromethamine administration.

Clinical Studies with Concomitant Use of Opioids

Clinical studies in postoperative pain management have demonstrated that ketorolac tromethamine-IV/IM, when used in combination with opioids, significantly reduced opioid consumption. This combination may be useful in the subpopulation of patients especially prone to opioid-related complications. Ketorolac tromethamine and narcotics should not be administered in the same syringe.

In a postoperative study, where all patients received morphine by a PCA device, patients treated with ketorolac tromethamine-IV as fixed intermittent boluses (e.g., 30 mg initial dose followed by 15 mg q3h), required significantly less morphine (26%) than the placebo group. Analgesia was significantly superior, at various postdosing pain assessment times, in the patients receiving ketorolac tromethamine-IV plus PCA morphine as compared to patients receiving PCA-administered morphine alone.

Postmarketing Surveillance Study

A large postmarketing observational, non-randomized study, involving approximately 10,000 patients receiving ketorolac tromethamine, demonstrated that the risk of clinically serious gastrointestinal (G.I.) bleeding was dose-dependent (see Table 3A and 3B). This was particularly true in elderly patients who received an average daily dose greater than 60 mg/day of ketorolac tromethamine (Table 3A).

TABLE 3

Incidence of Clinically Serious G.I. Bleeding as Related to Age, Total Daily Dose and History of G.I. Perforation, Ulcer, Bleeding (PUB) after up to 5 Days of Treatment with Ketorolac Tromethamine-IV/IM

A. Patients without History of PUB

	Total Daily Dose of Ketorolac Tromethamine-IV/IM			
Age of Patients	≤90 mg	>90 to 90 mg	>90 to 120 mg	>120 mg
<65 years of age	0.4%	0.4%	0.9%	4.6%
≥65 years of age	1.2%	2.8%	2.2%	7.7%

B. Patients with History of PUB

	Total Daily Dose of Ketorolac Tromethamine-IV/IM			
Age of Patients	≤90 mg	>90 to 90 mg	>90 to 120 mg	>120 mg
<65 years of age	2.1%	4.6%	7.8%	15.4%
≥65 years of age	4.7%	3.7%	2.8%	25.0%

INDICATIONS AND USAGE

Ketorolac tromethamine tablets are indicated for the short-term (≤5 days) management of moderately severe, acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Therapy should always be initiated with ketorolac tromethamine-IV/IM, and ketorolac tromethamine tablets are to be used only as a continuation treatment, if necessary. Combined use of ketorolac tromethamine-IV/IM and ketorolac tromethamine tablets is not to exceed 5 days of use because of the potential of increasing the frequency and severity of adverse reactions associated with the recommended doses (see WARNINGS, PRECAUTIONS, DOSAGE and ADMINISTRATION, and ADVERSE REACTIONS). Patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.

CONTRAINDICATIONS
(see also Boxed WARNING)

- Ketorolac tromethamine is CONTRAINDICATED in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding.
- Ketorolac tromethamine is CONTRAINDICATED in patients with advanced renal impairment, or in patients at risk for renal failure due to volume depletion (see WARNINGS for correction of volume depletion).
- Ketorolac tromethamine is CONTRAINDICATED in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine musculature, thus increasing the risk of uterine hemorrhage.
- The use of ketorolac tromethamine is CONTRAINDICATED in nursing mothers because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates.
- Ketorolac tromethamine is CONTRAINDICATED in patients with previously demonstrated hypersensitivity to ketorolac tromethamine, or allergic manifestations to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).
- Ketorolac tromethamine is CONTRAINDICATED as prophylactic analgesic before any major surgery, and is CONTRAINDICATED intraoperatively when hemostasis is critical because of the increased risk of bleeding.
- Ketorolac tromethamine inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis, and those at high risk of bleeding (see WARNINGS and PRECAUTIONS).
- Ketorolac tromethamine is CONTRAINDICATED in patients currently receiving ASA or NSAIDs because of the cumulative risks of inducing serious NSAID related adverse events.
- The concomitant use of ketorolac tromethamine and probenecid is CONTRAINDICATED.

WARNINGS
(see also Boxed WARNING)

The combined use of ketorolac tromethamine-IV/IM and ketorolac tromethamine tablets is not to exceed 5 days.

The most serious risks associated with ketorolac tromethamine are:

- **Gastrointestinal Ulcerations, Bleeding and Perforation:** Ketorolac tromethamine is contraindicated in patients with previously documented peptic ulcers and/or G.I. bleeding. Serious gastrointestinal toxicity, such as bleeding ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated with ketorolac tromethamine. Studies to date with NSAIDs have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Postmarketing experience with parenterally administered ketorolac tromethamine suggests that there may be a greater risk of gastrointestinal ulcerations, bleeding and perforation in the elderly.

  The incidence and severity of gastrointestinal complications increases with increasing dose of, and duration of treatment with, ketorolac tromethamine. In a non-randomized, in-hospital postmarketing surveillance study, comparing parenteral ketorolac tromethamine to parenteral opioids, higher rates of clinically serious G.I. bleeding were seen in patients <65 years of age who received an average total daily dose of more than 90 mg of ketorolac tromethamine-IV/IM per day (see CLINICAL PHARMACOLOGY - Postmarketing Surveillance Study).

  The same study showed that elderly (≥65 years of age), and debilitated patients are more susceptible to gastrointestinal complications. A history of peptic ulcer disease was revealed as another risk factor that increases the possibility of developing serious gastrointestinal complications during ketorolac tromethamine therapy (see Tables 3A and B).
- **Impaired Renal Function:** ***Ketorolac tromethamine should be used with caution in patients with impaired renal function, or a history of kidney disease because it is a potent inhibitor of prostaglandin synthesis.*** Renal toxicity with ketorolac tromethamine has been seen in patients with conditions leading to a reduction in blood volume and/or renal blood flow, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of ketorolac tromethamine may cause a dose-dependent reduction in renal prostaglandin formation and may precipitate acute renal failure. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of ketorolac tromethamine therapy is usually followed by recovery to the pretreatment state.

  Renal Effects: Ketorolac tromethamine and its metabolites are eliminated primarily by the kidneys, which, in patients with reduced creatinine clearance, will result in diminished clearance of the drug (see CLINICAL PHARMACOLOGY). Therefore, ketorolac tromethamine should be used with caution in patients with impaired renal function (see DOSAGE and ADMINISTRATION) and such patients should be followed closely. With the use of ketorolac tromethamine, there have been reports of acute renal failure, nephritis, and nephrotic syndrome.

  Because patients with underlying renal insufficiency are at increased risk of developing acute renal failure, the risks and benefits should be assessed prior to giving ketorolac tromethamine to these patients. Hence, in patients with moderately elevated serum creatinine, it is recommended that the daily dose of ketorolac tromethamine-IV/IM be reduced by half, not to exceed 60 mg/day. KETOROLAC TROMETHAMINE IS CONTRAINDICATED IN PATIENTS WITH SERUM CREATININE CONCENTRATIONS INDICATING ADVANCED RENAL IMPAIRMENT (see CONTRAINDICATIONS).

  Hypovolemia should be corrected before treatment with ketorolac tromethamine is initiated.
- **Fluid Retention and Edema:** Fluid retention, edema, retention of NaCl, oliguria, elevations of serum urea nitrogen and creatinine have been reported in clinical trials with ketorolac tromethamine. Therefore, ketorolac tromethamine should be used only very cautiously in patients with cardiac decompensation, hypertension, or similar conditions.
- **Hemorrhage:** Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet aggregation as well, use of ketorolac tromethamine in patients who have coagulation disorders should be undertaken very cautiously, and those patients should be carefully monitored. Patients on therapeutic doses of anticoagulants (e.g., heparin or dicumarol derivatives) have an increased risk of bleeding complications if given ketorolac tromethamine concurrently; therefore, physicians should administer such concomitant therapy only extremely cautiously. The concurrent use of ketorolac tromethamine and prophylactic low-dose heparin (2500 to 5000 units q 12h), warfarin and dextrans have not been studied extensively, but may also be associated with an increased risk of bleeding. Until data from such studies are available, physicians should carefully weigh the benefits against the risks, and use such concomitant therapy in these patients only extremely cautiously. In patients who receive anticoagulants for any reason, there is an increased risk of intramuscular hematoma formation from administered ketorolac-IM (see PRECAUTIONS - Drug Interactions). Patients receiving therapy that affects hemostasis should be monitored closely.

  In postmarketing experience, postoperative hematomas and other signs of wound bleeding have been reported in association with the perioperative use of ketorolac tromethamine-IV/IM. Therefore, perioperative use of ketorolac tromethamine should be avoided and postoperative use be undertaken with caution when hemostasis is critical (see WARNINGS and PRECAUTIONS).
- **Anaphylactoid Reactions:** Anaphylactoid reactions may occur in patients without a known previous exposure or hypersensitivity to aspirin, ketorolac tromethamine, or other NSAIDs, or in individuals with a history of angioedema, bronchospastic reactivity (e.g., asthma), and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

PRECAUTIONS

General

- **Hepatic Effects:** *Ketorolac tromethamine should be used with caution in patients with impaired hepatic function, or a history of liver disease.*

  Treatment with ketorolac tromethamine may cause elevations of liver enzymes, and in patients with pre-existing liver dysfunction it may lead to the development of a more severe hepatic reaction. The administration of ketorolac tromethamine should be discontinued in patients in whom an abnormal liver test has occurred as a result of ketorolac tromethamine therapy.
- **Hematologic Effects:** Ketorolac tromethamine inhibits platelet aggregation and may prolong bleeding time; therefore, it is contraindicated as a pre-operative medication and caution should be used when hemostasis is critical. Unlike aspirin, the inhibition of platelet function by ketorolac tromethamine disappears within 24 to 48 hours after the drug is discontinued. Ketorolac tromethamine does not appear to affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). In controlled clinical studies, where ketorolac tromethamine was administered intramuscularly or intravenously postoperatively, the incidence of clinically significant postoperative bleeding was 0.4% for ketorolac tromethamine compared to 0.2% in the control groups receiving narcotic analgesics.

Information for Patients

Ketorolac tromethamine is a potent NSAID and may cause serious side effects such as gastrointestinal bleeding or kidney failure, which may result in hospitalization and even fatal outcome.

Physicians, when prescribing ketorolac tromethamine, should inform their patients of the potential risks of ketorolac tromethamine treatment (see Boxed WARNING, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections). *Advise patients not to give ketorolac tromethamine tablets to other family members and to discard any unused drug.* Remember that the total duration of ketorolac tromethamine therapy is not to exceed 5 (five) days.

Drug Interactions

Ketorolac tromethamine is highly bound to human plasma protein (mean 99.2%).

The *in vitro* binding of ***warfarin*** to plasma proteins is only slightly reduced by ketorolac tromethamine (99.5% control vs. 99.3%) when ketorolac plasma concentrations reach 5 to 10 mcg/mL. Ketorolac does not alter ***digoxin*** protein binding. *In vitro* studies indicate that, at therapeutic concentrations of ***salicylate*** (300 mcg/mL), the binding of ketorolac was reduced from approximately 99.2% to 97.5%, representing a potential two-fold increase in unbound ketorolac plasma levels. Therapeutic concentrations of ***digoxin, warfarin, ibuprofen, naproxen, piroxicam, acetaminophen, phenytoin,*** and ***folibutaxside*** did not alter ketorolac tromethamine protein binding.

In a study involving 12 volunteers, ketorolac tromethamine tablets were co-administered with a single dose of 25 mg ***warfarin***, causing no significant changes in pharmacokinetics or pharmacodynamics of warfarin. In another study, ketorolac tromethamine-IV/IM was given with two doses of 5000 U of ***heparin*** to 11 healthy volunteers, resulting in a mean template bleeding time of 6.4 minutes (3.2 to 11.4 min) compared to a mean of 6.0 minutes (3.4 to 7.5 min) for heparin alone and 5.1 minutes (3.5 to 8.5 min) for placebo. Although these results do not indicate a significant interaction between ketorolac tromethamine and warfarin or heparin, the administration of ketorolac tromethamine to patients taking anticoagulants should be done extremely cautiously and patients should be closely monitored (see WARNINGS and PRECAUTIONS).

Ketorolac tromethamine-IV/IM reduced the diuretic response to ***furosemide*** in normovolemic healthy subjects by approximately 20% (mean sodium and urinary output decreased 17%).

Concomitant administration of ketorolac tromethamine tablets and ***probenecid*** resulted in decreased clearance of ketorolac and significant increases in ketorolac plasma levels (total AUC increased approximately 3-fold from 5.4 to 17.8 mcg/hr/mL) and terminal half-life increased approximately 2-fold from 6.6 to 15.1 hours. Therefore, concomitant use of ketorolac tromethamine and probenecid is contraindicated.

Inhibition of renal ***lithium*** clearance, leading to an increase in plasma lithium concentration, has been reported with some prostaglandin synthesis inhibiting drugs. The effect of ketorolac tromethamine on plasma lithium has not been studied, but cases of increased lithium plasma levels during ketorolac tromethamine therapy have been reported.

Concomitant administration of ***methotrexate*** and some NSAIDs has been reported to reduce the clearance of methotrexate, enhancing the toxicity of methotrexate. The effect of ketorolac tromethamine on methotrexate clearance has not been studied.

In post-marketing experience, there have been reports of a possible interaction between ketorolac tromethamine-IV/IM and ***non-depolarizing muscle relaxants*** that resulted in apnea. The concurrent use of ketorolac tromethamine with muscle relaxants has not been formally studied.

Concomitant use of ***ACE inhibitors*** may increase the risk of renal impairment, particularly in volume depleted patients.

Sporadic cases of seizures have been reported during concomitant use of ketorolac tromethamine and ***antiepileptic drugs*** (phenytoin sodium, carbamazepine).

Hallucinations have been reported when ketorolac tromethamine was used in patients taking ***psychoactive drugs*** (fluoxetine hydrochloride, thiothixene hydrochloride, alprazolam).

There is no evidence, in animal or human studies, that ketorolac tromethamine induces or inhibits hepatic enzymes capable of metabolizing itself or other drugs.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: An 18-month study in mice with oral doses of ketorolac tromethamine at 2 mg/kg/day (0.9 times the human systemic exposure at the recommended IM or IV dose of 30 mg q.i.d., based on area-under-the-plasma-concentration curve [AUC]), and a 24-month study in rats at 5 mg/kg/day (0.5 times the human AUC), showed no evidence of tumorigenicity.

Ketorolac tromethamine was not mutagenic in the Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. At 1590 mcg/mL and at higher concentrations, ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells.

Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg (0.9 times the human AUC) and 16 mg/kg (1.6 times the human AUC) of ketorolac tromethamine, respectively.

Pregnancy

Pregnancy - Category C: Reproduction studies have been performed during organogenesis, using daily oral doses of ketorolac tromethamine at 3.6 mg/kg (0.37 times the human AUC) in rabbits and at 10 mg/kg (1.0 times the human AUC) in rats. Results of these studies did not reveal evidence of teratogenicity to the fetus. Oral doses of ketorolac tromethamine at 1.5 mg/kg (0.14 times the human AUC), administered after gestation day 17, caused dystocia and higher pup mortality in rats. There are no adequate and well-controlled studies of ketorolac tromethamine in pregnant women. Ketorolac tromethamine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The use of ketorolac tromethamine is contraindicated in labor and delivery because, through its prostaglandin syntheses inhibitory effect, it may adversely affect fetal circulation and inhibit uterine musculature, thus increasing the risk of uterine hemorrhage (see CONTRAINDICATIONS).

Lactation and Nursing: After a single administration of 10 mg of ketorolac tromethamine tablets to humans, the maximum milk concentration observed was 7.3 ng/mL and the maximum milk-to-plasma ratio was 0.037. After one day of dosing (q.i.d.), the maximum milk concentration was 7.9 ng/mL and the maximum milk-to-plasma ratio was 0.025. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers is CONTRAINDICATED.

Pediatric Use: Safety and efficacy in pediatric patients (less than 16 years of age) have not been established. Therefore, use of ketorolac tromethamine in pediatric patients is not recommended.

Use in the Elderly (≥65 years of age): Because ketorolac tromethamine may be cleared more slowly by the elderly (see CLINICAL PHARMACOLOGY) who are also more sensitive to the adverse effects of NSAIDs (see WARNINGS - Renal Effects), extra caution and reduced dosages (see DOSAGE and ADMINISTRATION) must be used when treating the elderly with ketorolac tromethamine. The incidences and severity of gastrointestinal complications increases with the increasing dose of, and duration of treatment with, ketorolac tromethamine.

ADVERSE REACTIONS

Adverse reaction rates increase with higher doses of ketorolac tromethamine. Practitioners should be alert for the severe complications of treatment with ketorolac tromethamine, such as G.I. ulceration, bleeding and perforation, postoperative bleeding, acute renal failure, anaphylactic and anaphylactoid reactions, and liver failure (see Boxed WARNING, WARNINGS, PRECAUTIONS, and DOSAGE and ADMINISTRATION). These NSAID-related complications can be serious in certain patients for whom ketorolac tromethamine is indicated, especially when the drug is used inappropriately.

The adverse reactions listed below were reported in clinical trials as probably related to ketorolac tromethamine.

• INCIDENCE GREATER THAN 1%

(Percentage of incidence in parentheses for those events reported in 3% or more patients)

Body as a Whole: edema (4%).
Cardiovascular: hypertension.
Dermatologic: pruritus, rash.
Gastrointestinal: nausea (12%), dyspepsia (12%), gastrointestinal pain (13%), diarrhea (7%), constipation, flatulence, gastrointestinal fullness, vomiting, stomatitis.
Hemic and Lymphatic: purpura.
Nervous System: headache (17%), drowsiness (6%), dizziness (7%), sweating.

• INCIDENCE 1% OR LESS

Body as a Whole: weight gain, fever, infections, asthenia.
Cardiovascular: palpitation, pallor, syncope.
Dermatologic: urticaria.
Gastrointestinal: gastritis, rectal bleeding, eructation, anorexia, increased appetite.
Hemic and Lymphatic: epistaxis, anemia, eosinophilia.
Nervous System: tremors, abnormal dreams, hallucinations, euphoria, extrapyramidal symptoms, vertigo, paresthesia, depression, insomnia, nervousness, excessive thirst, dry mouth, abnormal thinking, inability to concentrate, hyperkinesis, stupor.
Respiratory: dyspnea, pulmonary edema, rhinitis, cough.
Special Senses: abnormal taste, abnormal vision, blurred vision, tinnitus, hearing loss.
Urogenital: hematuria, proteinuria, oliguria, urinary retention, polyuria, increased urinary frequency.

The following adverse events were reported from postmarketing experience.

Body as a Whole: hypersensitivity reactions such as anaphylaxis, anaphylactoid reaction, laryngeal edema, tongue edema (see Boxed WARNING, WARNINGS), myalgia.
Cardiovascular: hypotension and flushing.
Dermatologic: Lyell's syndrome, Stevens-Johnson syndrome, exfoliative dermatitis, maculo-papular rash, urticaria.
Gastrointestinal: peptic ulceration, GI hemorrhage, GI perforation (see Boxed WARNING, WARNINGS), melena, acute pancreatitis.
Hemic and Lymphatic: postoperative wound hemorrhage, rarely requiring blood transfusion (see Boxed WARNING, WARNINGS and PRECAUTIONS), thrombocytopenia, leukopenia.
Hepatic: hepatitis, liver failure, cholestatic jaundice.
Nervous System: convulsions, psychosis, aseptic meningitis.
Respiratory: asthma, bronchospasm.
Urogenital: acute renal failure (see Boxed WARNING, WARNINGS), flank pain with or without hematuria and/or azotemia, nephritis, hyponatremia, hyperkalemia, hemolytic uremic syndrome.

OVERDOSAGE

In controlled overdosage, daily doses of 360 mg of ketorolac tromethamine-IV/IM given for five days (3 times the highest recommended dose), caused abdominal pain and peptic ulcers which healed after discontinuation of dosing. Metabolic acidosis has been reported following intentional overdosage.

Dialysis does not significantly clear ketorolac tromethamine from the blood stream.

DOSAGE AND ADMINISTRATION

THE COMBINED DURATION OF USE OF KETOROLAC TROMETHAMINE-IV/IM AND KETOROLAC TROMETHAMINE TABLETS IS NOT TO EXCEED FIVE (5) DAYS. THE USE OF KETOROLAC TROMETHAMINE TABLETS IS ONLY INDICATED AS CONTINUATION THERAPY TO KETOROLAC TROMETHAMINE-IV/IM.

Ketorolac Tromethamine Tablets

Ketorolac tromethamine tablets are indicated ONLY as continuation therapy to ketorolac tromethamine-IV/IM for the management of moderately severe, acute pain that requires analgesia at the opioid level. See also PRECAUTIONS - Information for Patients.

Transition from Ketorolac Tromethamine-IV/IM to Ketorolac Tromethamine Tablets

The recommended ketorolac tromethamine tablet dose is as follows:

- Patients <65 years of age:
  Two (2) tablets as a first oral dose for patients who received 60 mg IM single dose, 30 mg IV single dose or 30 mg multiple dose ketorolac tromethamine-IV/IM followed by one (1) ketorolac tromethamine tablet every 4 to 6 hours, not to exceed 40 mg/24 hours of ketorolac tromethamine tablets.
- Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lbs) of body weight:
  One (1) tablet as a first oral dose for patients who received 30 mg IM single dose, 15 mg IV single dose or 15 mg multiple dose of ketorolac tromethamine-IV/IM followed by one (1) ketorolac tromethamine tablet every 4 to 6 hours, not to exceed 40 mg/24 hours of ketorolac tromethamine tablets.

Shortening the recommended dosing intervals may result in increased frequency and severity of adverse reactions.

The maximum combined duration of use (parenteral and oral ketorolac tromethamine) is limited to 5 days.

HOW SUPPLIED

Ketorolac Tromethamine Tablets USP are available as round, unscored, white, film-coated, black-printed tablets.

10 mg tablets (identified 54 033),
NDC 0054-8442-25: Unit dose, 10 tablets per strip, 10 strips per shelf pack, 10 shelf packs per shipper.
NDC 0054-4442-25: Bottles of 100 tablets.

Store bottles at controlled room temperature 15°-30°C (59°-86°F).
Store blister packages at controlled room temperature, 15°-30°C (59°-86°F). Protect from excessive humidity and light.

CAUTION: Federal law prohibits dispensing without prescription.

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Revised October 1996

Roxane Laboratories, Inc.
Columbus, Ohio 43216

BLISTER LABELS:

KETOROLAC TROMETHAMINE Tablet USP 10 mg LOT 950000 EXP. JAN. 1, 97 N 0054-8442-25 Roxane • Cols. OH	KETOROLAC TROMETHAMINE Tablet USP 10 mg LOT 950000 EXP. JAN. 1, 97 N 0054-8442-25 Roxane • Cols. OH
KETOROLAC TROMETHAMINE Tablet USP 10 mg LOT 950000 EXP. JAN. 1, 97 N 0054-8442-25 Roxane • Cols. OH	KETOROLAC TROMETHAMINE Tablet USP 10 mg LOT 950000 EXP. JAN. 1, 97 N 0054-8442-25 Roxane • Cols. OH
KETOROLAC TROMETHAMINE Tablet USP 10 mg LOT 950000 EXP. JAN. 1, 97 N 0054-8442-25 Roxane • Cols. OH	KETOROLAC TROMETHAMINE Tablet USP 10 mg LOT 950000 EXP. JAN. 1, 97 N 0054-8442-25 Roxane • Cols. OH
KETOROLAC TROMETHAMINE Tablet USP 10 mg LOT 950000 EXP. JAN. 1, 97 N 0054-8442-25 Roxane • Cols. OH	KETOROLAC TROMETHAMINE Tablet USP 10 mg LOT 950000 EXP. JAN. 1, 97 N 0054-8442-25 Roxane • Cols. OH
KETOROLAC TROMETHAMINE Tablet USP 10 mg LOT 950000 EXP. JAN. 1, 97 N 0054-8442-25 Roxane • Cols. OH	KETOROLAC TROMETHAMINE Tablet USP 10 mg LOT 950000 EXP. JAN. 1, 97 N 0054-8442-25 Roxane • Cols. OH

Usual Dosage: One tablet every 4 to 6 hours. See Package Insert for Complete Prescribing Information.

Store at Controlled Room Temperature 15°-30°C (59°-86°F) Protect from Excessive Humidity and Light.

Dispense in a tight, light-resistant container as defined in the USP/NF

TABLETS IDENTIFIED
54 033

NDC 0054-4442-25 100 Tablets

10 mg

KETOROLAC
Tromethamine
Tablets USP

Each tablet contains:
Ketorolac Tromethamine 10 mg
Caution: Federal law prohibits dispensing without prescription

Roxane Laboratories, Inc. Columbus, Ohio 43216

EXP LOT

JUN 27 1997

4178251
056
© RLI 1996

NDC 0054-8442-25 10 x 10 Tablets

10 mg

KETOROLAC
Tromethamine
Tablets USP

Each tablet contains:
Ketorolac Tromethamine 10 mg
Usual Dosage: One tablet every 4 to 6 hours. See Package Insert For Complete Prescribing Information.

Store at Controlled Room Temperature 15°-30°C (59°-86°F)
Do not remove blisters from carton prior to dispensing. Protect from Excessive Humidity and Light.

Blisters are not child-resistant. Use child-resistant closure if dispensing to outpatients.

Caution: Federal law prohibits dispensing without prescription.

TABLETS IDENTIFIED
54 033

© RLI. 1996

JUN 27 1997

NDC 0054-8442-25 **10 mg** 10 x 10 Tablets

KETOROLAC
Tromethamine
Tablets USP

LOT

EXP.

4254603

Roxane Laboratories, Inc. Columbus, Ohio 43216

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074790

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO 2 - revised to acknowledge that the labeling is now satisfactory

2. ANDA 74-790

3. NAME AND ADDRESS OF APPLICANT
Roxane Laboratories
Attention: Sue T. Bastaja
P.O. 16532
Columbus, OH 43216-6532

4. LEGAL BASIS FOR SUBMISSION
Toradol® Tablets, 10 mg (Syntex, NDA 19-645; US patent 4,089,969 was to expire 07/14/98, but now the Orange Book says 05/16/97 [not the first time it has changed!]).

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME Ketorolac Tromethamine Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES: see next page

10. PHARMACOLOGICAL CATEGORY
Nonsteroidal anti-inflammatory

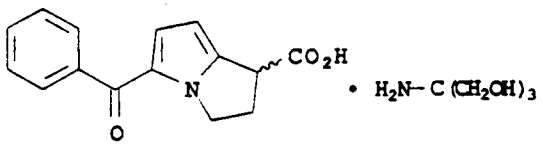
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM Tablets

14. POTENCY 10 mg

15. CHEMICAL NAME AND STRUCTURE
(±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)



$C_{15}H_{13}NO_3 . C_4H_{11}NO_3$ M.W. = 376.41 CAS [74103-07-4]

16. RECORDS AND REPORTS N/A

17. COMMENTS see next page

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend: Tentative APPROVAL.

19. REVIEWER: J. L. Smith DATE COMPLETED: 01/15/97

cc: ANDA 74-790
DUP File
Division File
Field Copy

Endorsements:
HFD-623/J.Smith/ 1/15/97
HFD-623/V.Sayeed, Ph.D./ 1/16/97
Y:\NEW\FIRMSNZ\ROXANE\LTRS&REV\74790AP2.D2
F/T by:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074790

BIOEQUIVALENCE REVIEW(S)

ANDA 74-790

Roxane Laboratories, Inc.
Attention: Sue T. Bastaja, R.Ph., J.D.
P.O. BOX 16532
Columbus OH 43216

APR 16 1996

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section [redacted] of the Federal Food, Drug and Cosmetic Act for Ketorolac Tromethamine Tablets USP, [redacted]

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 600 mL of water at 37°C using Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than [redacted] of the labeled amount of ketorolac in the tablet is dissolved in 45 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Ketorolac Tromethamine Tablets	Roxane Laboratories
10 mg Tablets	Columbus, Ohio
ANDA #74-790	Submission Date:
Reviewer: Moo Park	December 6, 1995
Filename: 74790sd.d95	

Review of a BE Study, Dissolution Data and a Waiver Request

I. Objectives

- Review of Roxane's two in vivo bioequivalence studies under fasting and non-fasting conditions comparing its Ketorolac Tromethamine Tablets, 10 mg, to Syntex's 10 mg Toradol[R] Tablets.

- Review of comparative dissolution data.

II. Background

Ketorolac is a non-steroidal anti-inflammatory drug (NSAID) that exhibits analgesic, anti-inflammatory, and antipyretic activity. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. Ketorolac is indicated for the short term management (up to 5 days) of pain. The recommended oral dose is 10 mg every 4 to 6 hours for a limited duration.

The pharmacokinetics of ketorolac in humans, following single or multiple oral doses, are apparently linear. Ketorolac is completely absorbed following oral administration with a mean peak plasma concentration of 0.7-1.1 ug/ml occurring an average of 44 minutes after a single 10 mg dose in fasted subjects. The terminal plasma half-life is 2.4-9 hrs in young adults and 4.3-7.6 hrs in the elderly. The primary route of excretion of ketorolac and its metabolites (conjugates and p-OH metabolite is in the urine (mean 91.4%) and the remainder (mean 6.1%) is excreted in the feces. A high fat meal has been shown to decrease the peak and to delay its appearance, but did not affect the extent of absorption.

III. Study Details

A. Study under fasting conditions

1. Protocol #10791

2. Applicant: Roxane Laboratories
Columbus, Ohio

3. Study sites:
   Clinical study:

   Analytical:

4. Investigators:
   Principal investigator:

   Analytical investigator:

5. Clinical study dates: 5/5/95-5/7/95 (Period 1)
   5/12/95-5/14/95 (Period 2)

   Assay dates: 5/22/95-5/30/95

6. Study design: Randomized, 2-treatment, 2-period, crossover bioequivalence study.

7. Subject: Twenty-six healthy male volunteers were recruited based on the acceptable results of medical histories, physical examinations, and laboratory tests.

8. Product information:

   (a) Test product: Roxane's Ketorolac Tromethamine Tablets, 10 mg strength.

   Lot #959015

   (b) Reference product: Syntex's Toradol^{R}, 10 mg strength.

   Lot #3706

9. Dosing: A single 10 mg dose with 240 mL of water.

10. Food and fluid intake: Subjects fasted overnight prior to the dosing and until 5 hours post-dose.

11. Housing: Subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until 24 hours post-dose each period.

12. Washout period: 7 days.

13. Blood samples: Ten mL of venous blood were obtained in Vacutainers with EDTA at: 0, 0.17, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 15, 18, and 24 hours post-

dose. Plasma was separated and promptly frozen at -20°C.

14. IRB and informed consent forms: Submitted.

15. Pharmacokinetic and statistical analysis: S A S - G L M procedures were used on AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el}, $t_{1/2}$ and blood levels at each sampling points. The 90% confidence intervals (CI) were calculated for log-transformed AUC_t, AUC_{inf} and C_{max}.

B. Study under non-fasting conditions

1. Protocol #10837A

2. Clinical study dates: 6/6/95-6/8/95 (Period 1)
6/13/95-6/15/95 (Period 2)
6/20/95-6/22/95 (period 3)

Assay dates: 6/22/95-6/26/95

3. Study design: Randomized, 3-treatment, 3-period, crossover bioequivalence study.

4. Subject: Eighteen healthy male volunteers were recruited based on the acceptable results of medical histories, physical examinations, and laboratory tests.

5. Product information:

(a) Test product under non-fasting: Roxane's Ketorolac Tromethamine Tablets, 10 mg strength.

Lot #959015

(b) Reference product under non-fasting: Syntex's Toradol^R, 10 mg strength.

Lot #3706

(c) Test product under fasting: Roxane's Ketorolac Tromethamine Tablets, 10 mg strength.

6. Dosing: A single 10 mg dose with 240 mL of water.

7. Food and fluid intake: Subjects assigned to treatment 3 fasted overnight prior to the dosing and until 5 hours post-dose. Subjects assigned to treatments #1 and 2 were served a standard breakfast 35 minutes prior to dosing.

8. Housing: Subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until 24

hours post-dose each period.

9. Washout period: 7 days.

10. Blood samples: Ten mL of venous blood were obtained in Vacutainers with EDTA at: 0, 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 15, 18, and 24 hours post-dose. Plasma was separated and promptly frozen at -20°C.

11. Pharmacokinetic and statistical analysis: SAS procedures were used on AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el}, $t_{1/2}$ and blood levels at each sampling points to calculated the test/reference ratios.

IV. Validation of Assay Method for Plasma Samples

V. In Vivo Results with Statistical Analysis

A. Study under fasting conditions

Twenty-six subjects enrolled and completed the study. It was found that for subject #22, the assay of the pre-dose samples without the addition of internal standard, revealed an interference at the retention time of the internal standard, in period 1. The data for subject #22 was not used in the statistical analysis.

The elimination rate constant (KE) for subject #25 could not be reliably estimated. AUCI was not calculated for the subject #25.

Five subjects experienced five adverse events (3 for test and 2 for reference product). All events were transient in nature and resolved spontaneously without medical intervention.

1. Mean plasma levels

The mean plasma ketorolac levels are comparable for the test and reference products as shown in Table 2 and Fig P-1. The mean peak concentrations were 883 ng/mL at 30 minutes and 878 ng/mL at 30 minutes, respectively, for the test and reference products.

Table 2. MEAN PLASMA KETOROLAC LEVELS FOR TEST AND REFERENCE PRODUCTS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.167	371.11	304.48	197.76	230.51	1.88
0.333	864.48	255.36	785.64	306.78	1.10
0.5	883.00	161.17	877.68	155.79	1.01
0.75	760.84	133.70	796.16	135.73	0.96
1	676.92	106.93	702.04	119.15	0.96
1.33	575.24	97.39	605.64	124.98	0.95
1.67	499.00	96.66	534.68	124.46	0.93
2	438.64	92.56	475.68	122.86	0.92
2.5	376.80	89.54	416.20	127.00	0.91
3	331.24	83.22	356.64	99.07	0.93
4	261.20	67.44	278.28	83.96	0.94
6	162.46	45.68	176.64	56.58	0.92
8	108.09	29.66	118.20	41.46	0.91
10	81.50	26.67	89.48	34.54	0.91
12	61.74	23.85	63.07	27.73	0.98
15	34.19	21.75	43.02	21.73	0.79
18	20.82	19.33	24.75	18.52	0.84
24	3.01	10.92	9.38	13.31	0.32

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Pharmacokinetic parameters

The pharmacokinetic parameters, AUCT, AUCI, and CMAX, are comparable for the test and reference products. The test/reference ratios (RMEAN12) for the non-transformed and log-transformed AUCT, AUCI, and CMAX range 0.93-1.04 as shown in Table 3.

The 90% confidence intervals for the log-transformed AUCT, AUCI, and CMAX are all within 80-125% range as shown in Table 4.

Table 3. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	3392.33	702.61	3600.84	958.29	0.94
AUCT	3139.44	639.53	3376.28	910.37	0.93
CMAX	975.84	163.23	944.96	176.20	1.03
KE	0.16	0.05	0.15	0.06	1.08
LAUCI*	3322.83	0.21	3470.47	0.28	0.96
LAUCT*	3077.04	0.21	3253.43	0.28	0.95
LCMAX*	962.39	0.17	929.36	0.19	1.04
THALF	4.76	1.47	5.34	1.84	0.89
TMAX	0.48	0.25	0.48	0.19	1.00

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

Table 4. LSMEANS AND 90% CONFIDENCE INTERVALS

PARAMETER	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
AUCI	3331.64	3596.02	87.50	97.80
AUCT	3139.78	3370.62	87.74	98.56
CMAX	976.33	945.78	96.36	110.10
LAUCI	3259.72	3465.96	89.33	99.02
LAUCT	3076.96	3248.27	89.74	99.99
LCMAX	962.48	930.17	96.53	110.92

B. Study under non-fasting conditions

Eighteen subjects participated in the study and four subjects dropped out. Subject #1 withdrew from the study in the 2nd period. Subject #12 failed to return for the 2nd and 3rd periods. Subject #3 failed to return to complete period 3. Subject #5 tested positive for cocaine in the 2nd period and was withdrawn from the study. Fourteen subjects were used for the pharmacokinetic and statistical evaluation.

subjects reported 6 adverse events (3 for test product and 3 for reference product). All events were mild and resolved without medical intervention.

1. Mean plasma levels

The plasma levels under non-fasting conditions were comparable for the test and reference products as shown in Table 5 and Fig P-2. The mean peak plasma levels were 422 ng/mL at 1.25 hours and 465 ng/mL at 1.5 hours, respectively, for the test and reference products as shown in Table 5.

Table 5. MEAN PLASMA KETOROLAC LEVELS FOR TEST AND REFERENCE PRODUCTS
MEAN1=TEST-FOOD MEAN2=REF-FOOD MEAN3=TEST-FASTING

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
0.333	217.65	192.91	134.14	206.78	831.36	321.14
0.67	342.57	181.31	350.29	250.32	826.93	155.15
1	397.14	166.01	416.64	226.42	690.57	140.53
1.25	421.86	152.54	442.71	200.59	615.07	135.34
1.5	419.71	125.79	465.00	176.01	556.86	116.51
1.75	406.57	101.13	462.14	156.19	509.93	113.11
2	413.43	91.69	452.79	115.41	476.07	112.41
2.5	398.57	101.00	445.29	95.01	397.36	97.99
3	381.21	88.61	411.79	98.23	344.79	98.32
4	336.29	99.93	355.93	103.89	278.93	86.78
6	213.07	64.84	237.00	75.06	181.79	56.20
8	134.15	49.86	151.89	54.03	124.16	57.05
10	96.46	37.57	104.34	41.49	94.51	34.65
12	73.19	31.19	79.46	36.03	72.04	29.51
15	41.19	24.74	45.57	28.06	41.10	21.87
[illegible]8	22.94	20.75	24.38	22.53	22.31	19.18
	7.56	12.45	8.58	14.40	5.98	12.14

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
0.333	1.62	0.26	0.16
0.67	0.98	0.41	0.42
1	0.95	0.58	0.60
1.25	0.95	0.69	0.72
1.5	0.90	0.75	0.84
1.75	0.88	0.80	0.91
2	0.91	0.87	0.95
2.5	0.90	1.00	1.12
3	0.93	1.11	1.19
4	0.94	1.21	1.28
6	0.90	1.17	1.30
8	0.88	1.08	1.22
10	0.92	1.02	1.10
12	0.92	1.02	1.10
15	0.90	1.00	1.11
18	0.94	1.03	1.09
24	0.88	1.26	1.43

Pharmacokinetic parameters

The test/reference ratios (RMEAN12) for non-transformed and log-transformed AUCT, AUCI and CMAX under non-fasting conditions ranged 0.91-0.94 as shown in Table 6.

Table 6. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION)

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
AUCI	3225.43	834.79	3480.86	1027.79	3604.14	1033.55
AUCT	3034.00	819.09	3270.50	963.51	3399.79	991.84
CMAX	519.79	114.39	573.57	151.53	949.71	206.80
KE	0.16	0.04	0.16	0.04	0.15	0.03
LAUCI	3127.37	0.26	3343.53	0.29	3483.06	0.26
LAUCT	2933.12	0.27	3140.13	0.30	3282.06	0.27
LCMAX	507.98	0.22	554.54	0.27	931.24	0.20
THALF	4.60	1.04	4.63	1.84	4.84	1.21
TMAX	1.95	1.13	2.03	1.13	0.45	0.17

(CONTINUED)

PARAMETER	RMEAN12	RMEAN13	RMEAN23
AUCI	0.93	0.89	0.97
AUCT	0.93	0.89	0.96
CMAX	0.91	0.55	0.60
KE	0.97	1.05	1.08
LAUCI	0.94	0.90	0.96
LAUCT	0.93	0.89	0.96
LCMAX	0.92	0.55	0.60
THALF	0.99	0.95	0.96
TMAX	0.96	4.31	4.50

VI. Product Information

1. Formulation

Test formulation for the 10 mg strength is shown in Table 7. The reference product contains lactose, microcrystalline cellulose and magnesium stearate as inactive ingredients.

Table 7. Formulation of Test Product

Ingredient	Amount per tablet, mg
Ketorolac Tromethamine USP	10
Microcrystalline Cellulose NF	
Lactose NF	
Magnesium Stearate NF	
Total weight	200

2. Assay ,content uniformity and batch size

Table 8. Assay, Content Uniformity and Batch Size

Product	Assay, %	Content uniformity, % (%CV)	Batch Size, tablets
Test, #959015	96.5	97.0 (1.3)	
Reference, #03706 Exp:12/96	95.6	95.5 (3.4)	-

VII. Dissolution

The following dissolution method was used:

Medium: 600 mL water
Apparatus 2 at 50 rpm
Tolerances: NLT (Q) in 45 min

Comparative dissolution data for the test and reference products met the dissolution specifications as shown in Table 9.

VIII. Waiver Request

None.

IX. Comments

1. Two *in vivo* bioequivalence studies were conducted under fasting and non-fasting conditions.

2. Study under fasting conditions: Twenty-six subjects enrolled and completed the study. Plasma samples for subject #22 revealed an interference at the time of the internal standard in period 1. The data for subject #22 was not used in the statistical analysis.

   Plasma levels at each sampling point and pharmacokinetic parameters were comparable for the test and reference products. The 90% confidence intervals for the log-transformed AUCT, AUCI, and CMAX are all within 80-125% range.

3. Study under non-fasting conditions: Eighteen subjects participated in the study and four subjects dropped out. The plasma levels at each sampling point for the test and reference product were comparable under non-fasting conditions. The test/reference ratios (RMEAN12) for non-transformed and log-transformed AUCT, AUCI and CMAX under non-fasting conditions ranged 0.91-0.94.

4. Assay method validations for the pre-study and within study are acceptable.

5. No clinically significant adverse events were reported during the two bioequivalence studies.

6. The batch size for the test product was tablets. Assay and content uniformity data are acceptable.

7. The *in vitro* dissolution data for the test product met the specifications.

X. Deficiency

None.

XI. Recommendations

1. The two *in vivo* bioequivalence studies conducted under fasting and non-fasting conditions by Roxane on its Ketorolac Tromethamine Tablets, 10 mg, lot #959015, comparing it to Syntex's Toradol[R] Tablets, 10 mg, Lot #03706, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Roxane's Ketorolac Tromethamine Tablets, 10 mg, is bioequivalent to the reference product, Syntex's Toradol[R] Tablets, 10 mg.

2. The dissolution testing conducted by Roxane on its Ketorolac Tromethamine Tablets, 10 mg, lot #959015, is acceptable.

3. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and the application is approvable.

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 600 mL of water at 37°C using Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of ketorolac in the tablet is dissolved in 45 minutes.

The firm should be informed of the recomendations.

Moo Park, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE 3/28/96

Concur: Date: 4/4/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

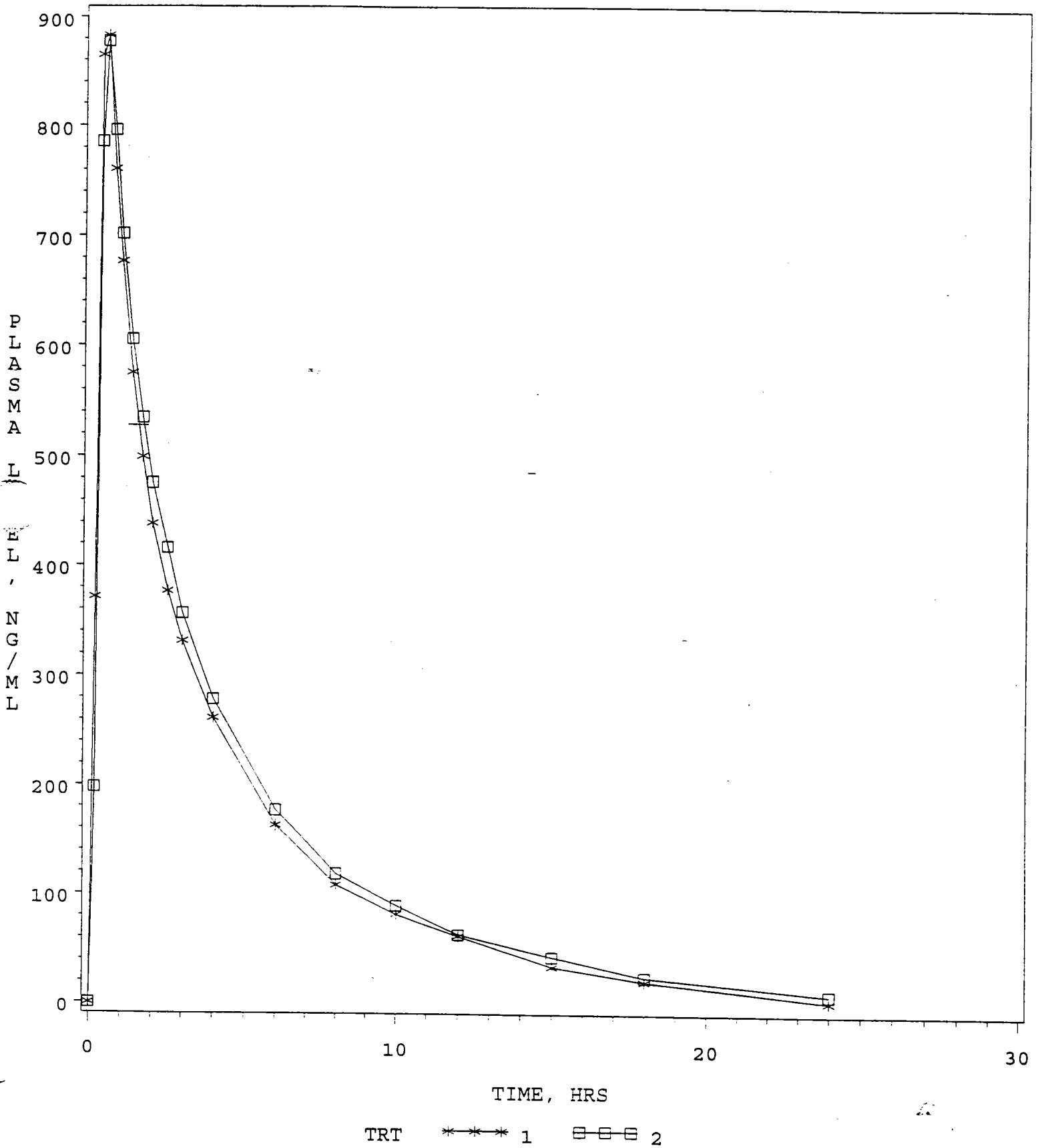
cc: ANDA # 74-790, HFD-630(OGD), HFD-604(Hare), HFD-658 (Mhatre, Park), HFD-22 (Hooton), HFC-130/JAllen, Drug File

File history: Draft (3/6/96); Final (3/26/96)

Table 9. *In Vitro* Dissolution Testing Data						
I. General Information						
Drug Product (Generic Name)	Ketorolac Tromethamine Tablets					
Strength	10 mg					
ANDA Number	74-790					
Applicant	Roxane					
Reference Drug Product	Syntex Toradol Tablets, 10 mg					
II. USP Method for Dissolution Testing						
Medium and Volume	600 mL water					
Apparatus and rpm	2 (paddle); 50 rpm					
Time	45 min					
Tolerances	(Q)					
Assay Method						
III. Dissolution Data (%)						
Time	Test Product Lot No:959015 Strength:10 mg No of Units:12			Reference Product Lot No:3706 Strength:10 mg No of Units:12		
Min	Mean	Range	%CV	Mean	Range	%CV
15	89		4.6	91		5.0
30	95		3.5	96		3.3
45	97		2.4	98		1.3

FIG P-1. PLASMA KETOROLAC LEVELS

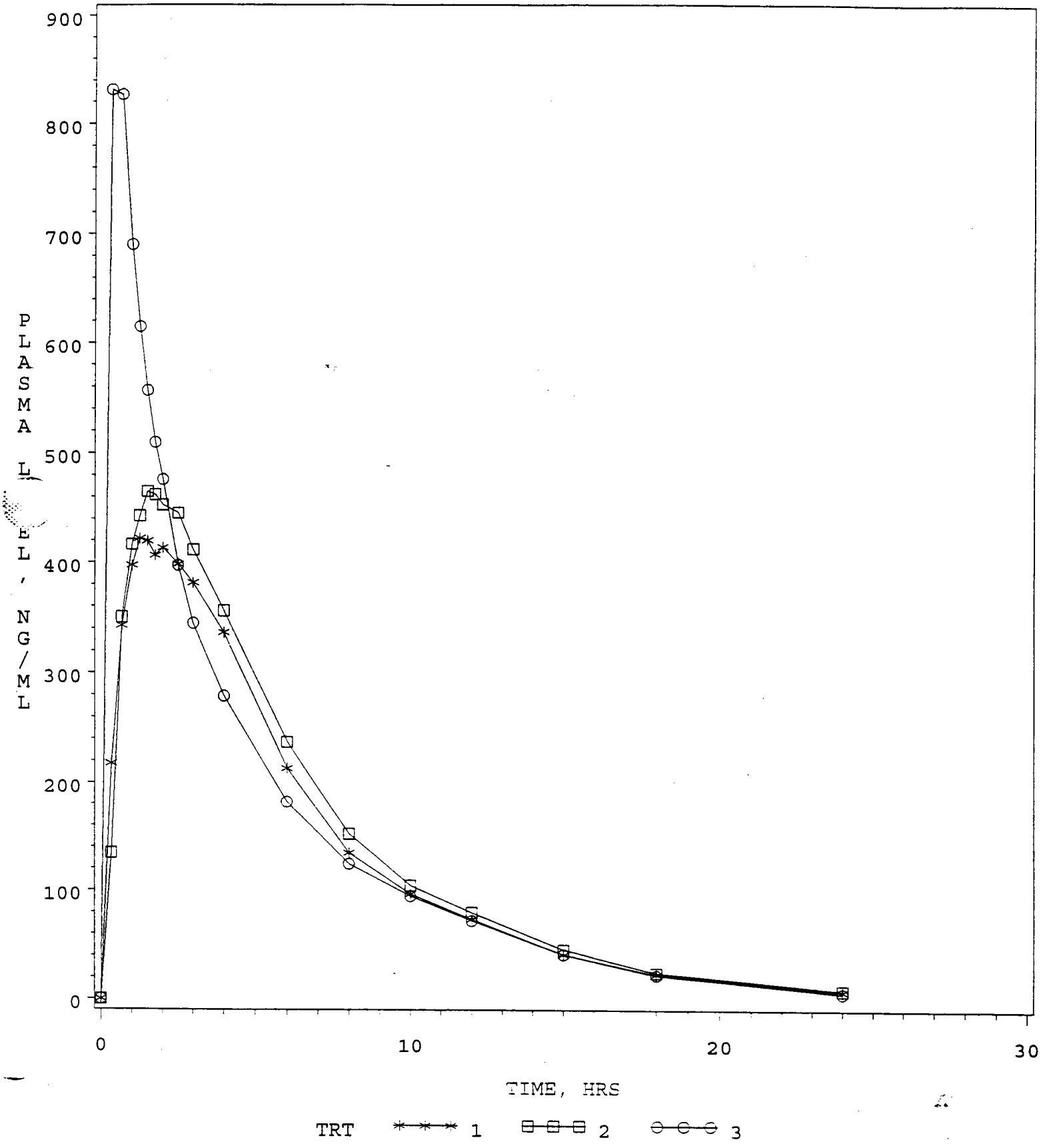
KETOROLAC TROMETHAMINE TABLETS, 10 MG, ANDA #74-790
UNDER FASTING CONDITIONS
DOSE=1 X 10 MG



1=TEST PRODUCT(ROXANE) 2=REFERENCE PRODUCT(SYNTEX)

FIG P-2. PLASMA KETOROLAC LEVELS

KETOROLAC TROMETHAMINE TABLETS, 10 MG, ANDA #74-790
UNDER NON-FASTING CONDITIONS
DOSE=1 X 10 MG



1=TEST PRODUCT-FOOD(ROXANE) 2=REFERENCE PRODUCT-FOOD SYNTEX) 3=TEST PRODUCT-FAST(ROXANE)